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10/588,574	05/31/2007	Stig Bengmark	05822.0340USWO	8316
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MERCHANT & GOULD PC			ARIANI, KADE	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/588,574	<b>Applicant(s)</b> BENCHMARK, STIG	
	<b>Examiner</b> KADE ARIANI	<b>Art Unit</b> 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 03 June 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 12-23 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 12-23 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

***DETAILED ACTION***

The amendment filed on June 03, 2008, has been received and entered.

Claims 1-11 have been canceled, and new claims 14-23 have been added.

Claims 12-23 are pending in this application and were examined on their merits.

***Claim Objection***

Claims 1, 3, and 7 have been cancelled therefore, the objection is withdrawn.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-11 have been cancelled therefore, the rejection of claims 1-13 under 35 U.S.C. 101, is withdrawn.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 12-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a mammal suffering from a stress-induced inflammatory disorder, does not reasonably provide enablement for preventing a stress-induced inflammatory disorder in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQd 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

#### The nature of the invention

The claims are drawn to a method for preventing or treating a stress-induced inflammatory disorder in a mammal. The invention is in a class of invention, which CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Micogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed Cir. 2001).

#### The breadth of the claims

The claims broadly encompass a method of preventing a stress-induced inflammatory disorder, lung inflammation, urinary inflammation, vaginal inflammation, bowel inflammation, stomach inflammation, liver inflammation, muscle inflammation, inflammation of endocrine and reproductive organs, and brain inflammation.

#### Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there are a significant number of inflammatory disorders that need to be examined. It would require significant number of studies to determine the effects of applying the claimed *Lactobacillus* strains and fibers in any one of these inflammatory disorders. This would require years of inventive effort, with each of the many inventing steps, not providing any guarantee of success in the succeeding steps.

#### The unpredictability of the art and the state of the prior art

The art is unpredictable with regard to prevention of a stress-induced inflammatory disorder by applying a probiotic and prebiotic formulation.

Chermesh et al. (Dig Dis Sci, 2007, Vol. 25, p.385-389) teach the failure of Synbiotic 2000, a cocktail containing 4 probiotic species (*Pediococcus pentoseceus*, *L. raffinolactis*, *Lactobacillus paracasei subsp paracasei* 19, and *Lactobacillus plantarum* 2362) and 4 prebiotics (2.5 g  $\beta$ -glucan, 2.5 g inulin, 2.5 g pectin, and 2.5 g resistant starch) to prevent postoperative recurrence of Crohn's disease (CD) an inflammatory

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disease of the gastrointestinal tract. Chermesh et al. teach a single dose of the synbiotic 2000 regiment was found to be ineffective in preventing postsurgical recurrence of CD. Chermesh et al. teach may exert their effect by changing the flora and thus be more effective in colonic disease (see Abstract, p.386 2nd column lines 1-8, and p.387-388 Discussion).

#### Working examples

In the specification, the multiple working examples are drawn to a method of treating trauma patients (transplant patients, patients undergoing abdominal cancer operations, patients with chronic liver disease, patients with cystic fibrosis, ...), and generally to the reduced incidence of secondary infection in the treated patients, and also to the reduction in neutrophil counts and activity of myeloperoxidase in experimental animals (with induced abdominal infection) supplemented with the formulation and not to preventing a stress-induced inflammatory disorder.

#### Guidance in the Specification

The specification does not teach how to use this method for preventing any and all types of inflammatory disorders.

#### Level of Skill in the Art

The level of skill in the art is deemed to be high, because of the complexity of the inflammatory disorders due to the involvement of multiple mediators.

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### Conclusion

Thus given the broad claims, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the negative teachings of the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written and the instant application does not support the breadth of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 has been cancelled therefore, the rejection of claim 3 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 12- 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monte (US 2003/0147857 A1) in view of Kruszewskya et al. (in IDS, Microecology and Therapy, 2002, Vol. 29, p.37-49) and further in view of Kaur et al. (European Journal of Pharmaceutical Sciences, 2002, Vol. 15, p.1-9) and further in view of Zhang et al. (JBC, 2002, Vol. 277, p.46116-46122).

Claims 12-23 are drawn to a method for preventing or treating a stress-induced inflammatory disorder in a mammal, comprising applying a formulation to the mammal, the formulation comprising *Pediococcus pentoseceus* 16:1(LMG P-20608), *Leuconostoc mesenteriodes* 23-77:1 (LMG P-20607), *lactobacillus paracasei* subsp *paracasei* F-19 (LMG P-17086), and *Lactobacillus plantarum* 2362 (LMG P-20606), wherein the bacterial strains are in an amount of at least  $10^{11}$  CFU/ml of each of the bacteria and at least four different fibers, the mammal is a human, stress-induced disorder is determined as an increase in neutrophils, cytokines, myeloperoxidases, four fibers are inulin, beta-glucan, pectin, and resistant starch (in an amount of 2.5 g each), vitamins, glutamine (amino acid), and the formulation is solid or liquid.

Monte teach a method for treating a mammal comprising applying a formulation to the mammal comprising probiotics and prebiotics, probiotics comprising *Pediococcus pentosaceus*, *lactobacillus paracasei*, and *Lactobacillus plantarum*, wherein the bacterial strains are in an amount of  $10^{10}$  or more of each of the bacteria, beta-glucan, inulin, pectins, resistant starch, vitamins, amino acids, and the formulation in form of tablet or drink (solid or liquid), and  $10^6$  or greater probiotic bacteria are introduced, and



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90-90% of prebiotics. Monte teaches probiotics are bacteria that benefit human health, particularly gastrointestinal health (Abstract, page 3 0025, 0028, 0030-0033, page 4 0039 (2<sup>nd</sup> column) 0046, and page 5 0050). Monte further teaches administration of antibiotics, exposure to gamma radiation and X-rays, disease, stress and other disturbances can result in an overgrowth of potentially pathogenic bacteria and/or a decrease in beneficial bacteria (p.2 0013). Monte further teaches certain strains of Lactobacilli have immune-modulating activity (p.2 0015 2<sup>nd</sup> column).

Monte does not teach *Pediococcus pentosaceus* 16:1(LMG P-20608), *Leuconostoc mesenteriodes* 23-77:1 (LMG P-20607), *lactobacillus paracasei* subsp *paracasei* F-19 (LMG P-17086), and *Lactobacillus plantarum* 2362 (LMG P-20606), and a stress-induced inflammatory disorder. However, Kruszewskya et al. teach *Pediococcus pentosaceus* 16:1, *Leuconostoc mesenteriodes* 77:1, *lactobacillus paracasei* subsp *paracasei* F-19, and *Lactobacillus plantarum* 2592 (Abstract, page 41 Table 2.). Kruszewskya et al. further teach exposure of *Lactobacillus* strains to pH 5 for 1 hour induced *de novo* production of several proteins, five of which cross-reacted with stress proteins and my protect other surface proteins and adhesions during transport (Abstract). Kruszewskya et al. teach production of antimicrobial substances with activity against other bacteria, induced induction of anti-inflammatory cytokines (IL-10) by *L. paracasei* subsp *paracasei* F-19, and teach, *Lactobacillus plantarum* 2592, *Pediococcus pentosaceus* 16:1, produced antioxidants which provide beneficial effects in scavenging free radicals (Abstract and p.45 1<sup>st</sup> and 2<sup>nd</sup> columns). The LAB strains taught by

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Kruszewskya et al. are the same or obvious variants of the claimed *Lactobacillus* strains.

Moreover, Kaur et al. teach immunomodulation by probiotics (p.5 1<sup>st</sup> and 2<sup>nd</sup> columns). Kaur et al. teach a probiotic preparation (a combination of probiotics, multiple strains) for treating ulcerative colitis (stress-induced inflammation) (p.4 Table 1. VSL#3). Kaur et al. further teach synbiotics (a mixture of probiotics and prebiotics) overcome the limitations of probiotics, and improve the survival and implantation of live microbial dietary supplement (p.7 2<sup>nd</sup> column 2<sup>nd</sup> paragraph).

Furthermore, Zhang et al. teach a characteristic feature of inflammation is the peroxidation of lipids and formation of lipid peroxidation products, which has been linked to cellular dysfunction. Zhang et al. teach myeloperoxidase (MPO) major role in formation of bioactive lipid oxidation products and promoting oxidative stress during inflammation (see Abstract and Introduction, p.46121 1<sup>st</sup> column end paragraph and 2<sup>nd</sup> column lines 1-4).

Therefore, in view of the above teachings, it would have been obvious to one of the ordinary skill in the art to combine the prior art teachings and to use *Lactobacillus* strains as taught by Kruszewskya et al. in the methods as taught by Monte with predictable results in order to provide a method for treating a stress-induced inflammatory disorder comprising applying to the mammal a formulation comprising *Pediococcus pentosaceus* 16:1, *Leuconostoc mesenteriodes* 23-77:1, *Lactobacillus paracasei subsp paracasei* F-19, and *Lactobacillus plantarum* 2362, and fibers (prebiotics) to provide an improved method with predictable results. The motivation to

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apply a formulation comprising probiotics and prebiotics for preventing a stress-induced disorder as taught by Kruszewskya et al. and Kaur et al. would be the production of anti-inflammatory cytokines and antioxidants by the probiotic strains

### ***Response to Arguments***

Applicant's arguments filed on 06/03/2008 have been fully considered but they are not persuasive.

Applicant argues that claims 12-23 are not obvious because the cited references do not teach or suggest each of the specific bacterial strains, and that Kruszewskya et al. disclose *Lactobacillus plantarum* 2592 and not the *Lactobacillus plantarum* 2362.

However, as mentioned immediately above, Kruszewskya et al. teach *Pediococcus pentosaceus* 16:1, *Leuconostoc mesenteroides* 77:1, *Lactobacillus paracasei subsp paracasei* F-19, and *Lactobacillus plantarum* 2592 (Abstract, page 41 Table 2. Moreover, the LAB strains taught by Kruszewskya et al. are the same or in the case of *Lactobacillus plantarum* 2592, an obvious variant of the claimed LAB strains. Thus, Kruszewskya et al. teach and suggest the claimed LAB strains.

Applicant argues that Monte does not recite that the prebiotic and probiotic formulation can be utilized to prevent and/or treat a stress-induced inflammatory disorder in a mammal.

However, the selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). In this case the anti-

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inflammatory and antioxidant properties exerted by the probiotic strains support the suitability of the strains for their intended use, which is to treat a stress-induced inflammatory disorder. Moreover, Kruszewskya et al. teach treatment studies in patients with inflammatory bowel disease have been encouraging particularly in patients with ulcerative colitis (p.38 2<sup>nd</sup> column 1<sup>st</sup> paragraph). Therefore, a person of ordinary skill in the art at the time the invention was made could have been motivated to include a probiotic strain(s) that produce anti-inflammatory molecules in a formulation for treating a stress-induced inflammatory disorder with predictable results.

Moreover, as mentioned immediately above, Zhang et al. teach a characteristic feature of inflammation is the peroxidation of lipids and formation of bioactive lipid peroxidation products at the site of inflammation. Therefore, a person of ordinary skill in the art at the time the invention was made could have been motivated to include a probiotic strain(s) that produce antioxidants in a formulation for treating a stress-induced inflammatory disorder with predictable results.

### ***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/  
Primary Examiner, Art Unit 1651

Kade Ariani  
Examiner  
Art Unit 1651